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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,099	09/26/2001	Michael Neal Blackburn	P50438-1	5739

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EXAMINER
DUFFY, PATRICIA ANN

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/965,099	Blackburn.
Examiner	**Group Art Unit**
Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 1-27-03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-20 is/are pending in the application.

Of the above claim(s) 14-16 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-13 + 17-20 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 1-20 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 10

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. Applicants response filed 1-27-03 has been entered into the record. Claims 1-20 are pending.

Priority

2. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be updated. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Election/Restriction

3. Applicant's election with traverse of Group I, species A in Paper No. 13 is acknowledged. The traversal is on the ground(s) that the anti-factor IXa antibody is a reagent that targets a component of the intrinsic coagulation pathway and therefore an anti-factor IX antibody is a member of the genus of reagents that are administered when practicing the invention of claim 14 and therefore the examiners Group I represents a subgenus of Group II. This is not found persuasive because the art teaches that intrinsic pathway comprises 4 main proteins Factor XII, prekallikrein, high molecular weight Kininogen and coagulation factor XI (see Paul et al, Fundamental Immunology 1989, page 276, paragraph bridging columns 1-2). Factor IX is a component of both the extrinsic and the intrinsic coagulation pathways. Factor IX is also activated by the extrinsic pathway of coagulation (tissue factor complex (Methods in Enzymology, Vol 222, page 177)). Therefore, Factor IX is not a "specific" target of the intrinsic coagulation pathway. The

argued monoclonal antibody does not "specifically target" a component of the intrinsic coagulation pathway, inasmuch as Factor IX/IXa are NOT specific to the intrinsic coagulation pathway. Therefore, applicants arguments are not persuasive in view of the recitation of "specifically targeting" in the claims of Group II.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Specification

5. The title of the invention is not descriptive of the claimed invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 U.S.C. § 112

6. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting thrombosis in an animal comprising administering an dose of anti-Factor IX monoclonal antibody having self-limiting neutralizing activity effective to inhibit thrombosis in combination with a plasminogen activator, does not reasonably provide enablement for inhibiting thrombosis using any antibody that binds any coagulation factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to the administration of any anti-coagulation factor monoclonal antibody having self-limiting neutralizing activity in combination with a

plasminogen activator in order to inhibit thrombosis in an animal. The teachings of the specification are limited to the demonstration of an anti-Factor IX monoclonal antibody having self-limiting neutralizing activity alone or in combination with tPA in order to inhibit thrombosis in an animal. Neither the art, nor the specification teach that all other claimed anti-coagulation monoclonal antibodies have (a) self-limiting neutralizing activity and (b) have the ability to inhibit thrombosis as instantly claimed. The different coagulation factors perform different functions in different portions of the coagulation cascade. All coagulation factors are not equivalent. Compensation of one part of the cascade when the other is defective or has lower activity has been documented in the art. However, such compensation is particular to the Factors involved. Applicants admit at page 64 line 1-10, that in a model of thrombosis the effect "... is significantly dependent on which anti-coagulant was administered with the thrombolytic.". The art of record teaches fibrinolytic agents such as tPA, APSAC, urokinase, TNK-tPA have different dosing regimens and have different effective doses. In view of the different effects on patency of the different fibrinolytic agents and in view of the lack of teachings of the specification, is not readily apparent that the teachings for the combination of anti-Factor IX monoclonal antibody in combination with tPA has broad applicability to all anti-coagulation factor monoclonal antibodies having self-limiting neutralizing activity and thrombolytic agents as are instantly claimed. Therefore, the teachings of a particular species does not extrapolate to the genus now claimed, in the absence of evidence that the findings for tPA are generic to the subgenus of plasminogen activators and the teachings for anti Factor IX monoclonal antibody having self-limiting neutralizing activity for the genus of anti-coagulation factor antibodies.

7. Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing a required dose of tPA comprising administering an anti-Factor IX monoclonal antibody in combination with tPA, does not reasonably provide enablement for a method of reducing a required dose of any thrombolytic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of reducing a required dose of a thrombolytic agent comprising administering an anti-Factor IX monoclonal antibody in combination with the thrombolytic agent. The teachings of the specification are limited to the demonstration that Anti-Factor IX monoclonal antibody lowers the required dose of the plasminogen activator, tPA, to restore patency in an art accepted model of reperfusion thrombosis. Applicants admit at page 64 line 1-10, that the "..incidence of reperfusion is significantly dependent on which anti-coagulant was administered with the thrombolytic.". The art of record teaches fibrinolytic agents such as tPA, APSAC, urokinase, TNK-tPA have different dosing regimens and have different effective doses. In view of the different effects on patency of the different fibrinolytic agents and in view of the teachings of the specification, is not readily apparent that the teachings for the combination of anti-Factor IX monoclonal antibody in combination with tPA has broad applicability to all thrombolytic agents as are instantly claimed. Therefore, the teachings of a particular species does not extrapolate to the genus now claimed, in the absence of evidence that the findings for tPA are generic to the subgenus of plasminogen activators or the genus of fibrinolytic agents.

8. Claims 1-13, 18, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 1-13, the phrase "effective amount" renders the claim indefinite because it is not clear from the claim construction what effect is achieved by the amount.

As to claims 5, 6, 18 and 19, the claims are rendered indefinite from the use of the term "..the monoclonal antibody has the identifying characteristics of ..." because it is unclear what the identifying characteristics of the recited monoclonal antibodies are particularly claimed. This rejection may be obviated by reciting ".. the monoclonal antibody having all the identifying characteristics of...". Should applicants amend the claims as recited, a deposit for patent purposes will be required because, the particular antibodies will be required to determine if the antibodies have all the identifying characteristics as those particular hybridomas.

Claim Rejections - 35 U.S.C. § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made

absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. It is noted that the instantly claimed invention drawn to methods of inhibiting thrombosis in an animal comprising administering an effective dose of anti-coagulation factor monoclonal antibody having self-limiting neutralizing activity in combination with a plasminogen activator, lacks written description in the parent application 08/783,853. Should Applicants wish to contest this, then applicants are invited to point to the parent '853 application where written description support for the claimed subject matter can be found. The filing date for prior art purposes is therefore the filing date of parent application 09/346,487, filed 7-1-99.

11. Claims 1-2 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kessler (Chest, 99(Suppl 4):9112S, April 1991) in view of Ruf et al (Thrombosis and Haemostasis, 66(5):529-533, 1991).

Kessler teaches that the goal of current modern treatment of cardiopulmonary disease is predicated on the goal of dissolving the offending clot to establish vascular patency and preventing rethrombosis using anti-coagulants combination of anti-coagulative agents with lytic agents (see page 97S, column 1 abstract). Kessler teaches that similar therapies have been employed in the treatment of coronary artery thrombosis, pulmonary embolism and peripheral arterial occlusion. Kessler also teaches that when anti-coagulants or anti-platelet-aggregating agents are used sequentially or concomitantly as adjunctives to thrombolytic therapy, they appear to enhance its efficacy. Kessler et al teach the

combination of aspirin, heparin or coumarin in combination with thrombolytic agents such as tPA, streptokinase, and urokinase to treat thrombolytic disease (see for example page 101S, column 2, second full paragraph, page 102S column 1 and page 105S, column 2, second full paragraph). Kessler et al teach that the extrinsic pathway of coagulation activated by tissue factor or tissue thromboplastin can be monitored by the prothrombin time determination. Kessler teaches that tissue factor can be activated by factor IXa (see page 103S, column 2, last paragraph). Kessler differs by not teaching the administration of a monoclonal antibody against a coagulation factor or Factor IX/IXa in particular to inhibit coagulation or rethrombosis.

Ruf et al teach anti-tissue factor monoclonal antibodies that inhibit TF-VIIa complex are potent anticoagulants. Ruf et al teach that the monoclonal antibody introduces a therapeutic principle for rapid arrest of inappropriate triggering of coagulation by tissue factor (page 529, summary). Ruf et al teach that these antibodies appear to possess therapeutic potential as exemplified by their capacity to provide prophylactic protection in the lethal *E. coli* septic shock model in baboons (page 529, paragraph bridging columns 1-2). Ruf et al teaches that the various specific and rapid inhibitors of TF-VIIa function in the extrinsic pathway have use in as tools for the study of the extrinsic pathway as well as therapeutic intervention in various states of disease (page 532, column 2).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute the coagulation inhibiting monoclonal antibody of Ruf et al for any one aspirin, heparin or coumarin in the treatment combination with thrombolytic agents such as tPA, streptokinase, and urokinase to treat thrombolytic disease because Kessler et al teach goal of current modern treatment of cardiopulmonary

disease is predicated on the goal of dissolving the offending clot to establish vascular patency and preventing rethrombosis using anti-coagulants combination of anti-coagulative agents with lytic agents (see page 97S, column 1 abstract) and because Kessler also teaches that when anti-coagulants or anti-platelet-aggregating agents are used sequentially or concomitantly as adjunctives to thrombolytic therapy, they appear to enhance its efficacy. The substitution of one anticoagulant for another in the combination therapy for treatment of any thrombolytic disease is *prima facie* obvious.

12. Claims 1-13 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kessler (Chest, 99(Suppl 4):9112S, April 1991) and Ruf et al (Thrombosis and Haemostasis, 66(5):529-533, 1991) as applied to claims 1-2 and 7-11 above and further in view of Seth et al (Blood et al., 92(10 Suppl. 1, Part 1-2), p 362A, November 15, 1998).

The combination of Kessler (Chest, 99(Suppl 4):9112S, April 1991) and Ruf et al (Thrombosis and Haemostasis, 66(5):529-533, 1991) is set forth supra. The combination differs by not using a monoclonal antibody that binds Factor IX or Factor IXa.

Seth et al teach that administration of a humanized monoclonal antibody SB 249417 to healthy volunteers. Seth et al teach that antibody binding inhibits activation of factor IX and also blocks the activity of Factor Xa on FX. Seth et al teach the anticoagulant activity of SB 249417 was demonstrated by dose dependent increases in aPTT and ACT. Seth et al teach that SB 249417 may provide a new long acting anti-thrombolytic agent.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the humanized monoclonal antibody of Seth et al for the anticoagulant monoclonal antibody of Ruf et al in the method of treatment of thrombosis as combined *supra* because Seth et al teaches that the humanized monoclonal antibody increases aPTT (i.e. inhibiting coagulation) and Kessler teaches that the extrinsic

pathway of coagulation is monitored by the prothrombin time determination and that factor IX/IXa (see page 103S, column 2, last paragraph) participates in the coagulation by the extrinsic pathway. One would have been motivated to substitute the antibody of Seth et al in the method as combined because Seth et al teaches that the humanized antibody inhibits coagulation as assessed by a prolongation of aPTT and ACT and Kessler et al teaches combination of agents enhance the efficacy of lytic agents.

Status of Claims

13. No claims are allowed. All claims stand rejected.

Citation of Pertinent Art

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bajaj et al," Human Factor IX and Factor IXa", in Methods in Enzymology, Volume 222, Part A, pages 96-128 and 177, 1993 is cited to teach the structure and function of coagulation Factor IX and its function in all pathways of coagulation.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to

3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
January 16, 2001

Pat a. Duffy

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600